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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TREATMENT OF DIABETES

(57) Abstract: Compositions and methods are provided for islet neogenesis therapy comprising a member of a group of factors that complement a gastrin/CCK receptor ligand, with formulations, devices and methods for sustained release delivery and for local delivery to target organs.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/33595

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 38/18, 26
US CL : 514/12
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/12; 530/308,309

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST, MEDLINE, STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 02/055152 A2 (WARATAH PHARMACEUTICALS, INC.) 18 July 2002 (18.07.2002), page 9, line 26; page 10, line 32 to page 11, line 4; page 11, lines 17-20; page 12, line 31; page 13, lines 3-19; page 14, lines 4-14 and 23; page 15, lines 9-24 and 27-30.	48, 50, 51, 53-58, 61-64, 66, 67, 69-71 --- 1-3, 7-10, 13, 14, 16-20, 24, 25, 45, 52, 59, 60, 65, 68, 91, 92, 101
Y	US 6,284,727 B1 (KIM et al) 4 September 2001 (04.09.2001), column 1, lines 8-13; column 16, line 61 to column 17, line 7.	1-3, 7-10, 13, 14, 16-20, 24, 25, 45, 52, 91, 92, 101
Y	US 2001/0024824 A1 (MOSS et al) 27 September 2001 (27.09.2001), paragraphs 346 and 358-361.	59, 60, 65, 68
Y	ROOMAN, I. Gastrin stimulates B-cell Neogenesis and Increases Islet Mass From Transdifferentiated but Not from Normal Exocrine Pancreas Tissue. Diabetes. March 2002, Vol. 51, pages 686-690, entire document.	1-3, 7-10, 13-14, 24, 25, 91, 92, 101

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US03/33595

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.: none
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 82 and 90
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 82 is dependent on itself. Claim 90 is listed twice as different claims.

3. ☒ Claim Nos.: 77-81,83-86,99,100 and 105-107
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-3,7-10,13,14,16-20,24,25,45,48,50-71,91,92 and 101

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/33595

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-4, 7-10, 12-14, 16-20, 24-26, 45, 48, 50-71, 91-98, 101-103, and 110, in so far as they are drawn to a method for treating diabetes, or a method of inducing pancreatic islet neogenesis, with a gastrin/CCK receptor ligand that is gastrin-17, a FACGINT that is GLP-1; and compositions and kits thereof.

Group II, claims 5-11, 15, and 24-26, in so far as they are drawn to a method for treating diabetes comprising ex vivo cell treatment with a gastrin/CCK receptor ligand that is gastrin-17 and a FACGINT that is GLP-1, and an immunosuppressive drug that is rapamycin, followed by administration to a mammal.

Group III, 21-31 and 108, in so far as they are drawn to a method for expanding and differentiating stem cells into insulin secreting cells in a diabetic recipient of implanted cells, or a method of expanding a functional β cell mass of pancreatic islet transplants in a diabetic receipient of purified islets, comprising implanting stem cells and administering a composition comprising a gastrin/CCK receptor ligand that is gastrin-17 and a FACGINT that is GLP-1.

Group IV, 32-45, in so far as they are drawn to a method for reducing an amount of stem cells needed for transplantation to treat human diabetes, comprising administering a gastrin/CCK receptor ligand that is gastrin-17, a FACGINT that is GLP-1, and an immunosuppressive drug that is rapamycin.

Group V, 46, 47 and 49, in so far as they are drawn to a kit or pharmaceutical composition comprising an immunosuppressive drug that is rapamycin, a FACGINT that is GLP-1, and with or without a gastrin receptor ligand.

Group VI, claims 72-76, in so far as they are drawn to a method of reducing frequency of treating a diabetic subject by administering an I.N.T. composition.

Group VII, claims 87-89, in so far as they are drawn to a method of treating a diabetic subject by providing a device to the subject.

Group VIII, claim 104, drawn to a method of treating a diabetic subject comprising administering a gastrin/CCK receptor ligand that is gastrin-17, a FACGINT that is GLP-1, and an agent for immune suppression.

Group IX, claim 109, drawn to a method of treating diabetes comprising transplanting a pancreatic islet preparation into a diabetic patient and administering an effective dose of a gastrin/CCK receptor ligand that is gastrin-17 and a FACGINT that is GLP-1.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

a) The 1st species of a gastrin/CCK receptor ligand is gastrin-17 and the 2nd to 3rd species are gastrin 1-17Leu15, or another specific gastrin.

The claims correspond to the species listed in the following manner:
Claims 25 correspond to the species of gastrin-17.
Claims 26 and 98 correspond to the species of gastrin 1-17Leu15.
The following claim(s) are generic: 1-24, 27-45, 48-62, 64-75, 87-89, 91-98, 101-104, and 108-110.

b) The 1st species of a FACGINT that is not an EGF receptor is GLP-1 and the 2nd to 29th species are exendin-4; a Growth Hormone; another Glucagon-like peptide 1 receptor ligand, a Glucagon-like peptide 2 receptor ligand; a gastric inhibitory polypeptide (GIP)

receptor ligand; a keratinocyte growth factor (KGF) receptor ligand; a dipeptidyl peptidase IV inhibitor; a REG protein receptor ligand; a Growth Hormone receptor ligand; a prolactin receptor ligand ; an Insulin-like Growth Factor (IGF) receptor ligand; PTH-related protein (PTHrP) receptor ligand; hepatocyte growth factor (HGF) receptor ligand, a bone morphogenetic protein (BMP) receptor ligand, a transforming growth factor-β (TGF-β) receptor ligand; a laminin receptor ligand; vasoactive intestinal peptide (VIP) receptor ligand; a fibroblast growth factor (FGF) receptor ligand; a keratinocyte growth factor receptor ligand; a nerve growth factor (NGF) receptor ligand; an islet neogenesis associated protein IINGAPI receptor ligand; an Activin-A receptor ligand; a vascular 20 endothelial growth factor (VEGF) receptor ligand; an erythropoietin (EPO) receptor ligand; a pituitary adenylate cyclase activating polypeptide (PACAP) receptor ligand, a granulocyte colony stimulating factor (G-CSF) receptor ligand; a granulocyte- macrophage colony stimulating factor (GM-CSF); a platelet-derived growth factor (PDGF) receptor ligand; and a Secretin receptor ligand.

The claims correspond to the species listed above in the following manner:
Claims 3, 91-92, 98, 101 and 104 correspond to the species of GLP-1.
Claim 3, 91, 101 and 104 correspond to the species of exendin-4.
Claims 4, 93-94, 98, 102 and 104 correspond to the species of Growth Hormone.
Claims 96-98, 103-104, and 110 correspond to the species of prolactin receptor ligand.
Claims 2 and 52 correspond to multiple species listed above.
The following claim(s) are generic: 1, 5-75, 87-89, and 108-109.

c) The 1st species of a measuring parameter is blood glucose and the 2nd to 10th species are serum glucose, blood glycosylated hemoglobin, pancreatic cell mass, serum insulin, pancreatic insulin content, and morphometrically determined β cell mass, amount of insulin secreting cells, glucose responsiveness of insulating secreting cells, amount of proliferation of islet precursor cells, and amount of mature insulin secreting cells.

The claims correspond to the species listed above in the following manner:
Claim 9 corresponds to the species of blood glucose.
Claims 10 and 12 correspond to multiple species listed above.
The following claim(s) are generic: none

d) The 1st species of an agent for suppressing immune response is rapamycin and the 2nd to 33rd species are a corticosteroid; an azathioprine; mycophenolate mofetil; a cyclosporine; a cyclophosphamide; a methotrexate; a 6-mercaptopurine; FK506, 15-deoxyspergualin; an FTY 720, a mitoxantrone, a 2-amino-1,3-propanediol; a 2-amino-2[2-(4- octylphenyl)ethyl]propane-1,3-diol hydrochloride; a 6-(3-dimethyl-aminopropionyl) forskolin; demethimmunomycin; hul 124, BTI- 322, allotrap-HLA-B27O; OKT4A, Enlimomab; ABX-CBL; OKT3; ATGAM; basiliximab; daclizumab, thymoglobulin; ISAtx247, Medi-500; Medi-507; Alefacept, efalizumab; infliximab; or an interferon.

The claims correspond to the species listed above in the following manner:
Claims 34-38 and 44 correspond to multiple species listed above.
The following claim(s) are generic: 33, 39-43, 46-47, 49, and 104

e) The 1st species of implanted cell is pancreatic islets and the 2nd to 4th are umbilical chords, embryos, and stem cell lines.

The claims correspond to the species listed above in the following manner:
Claim 23 corresponds to each of the species listed above.
The following claim(s) are generic: 21

f) The 1st species of EGF receptor ligand is EGF and the 2nd is TGFα.

The claims correspond to the species listed above in the following manner:
Claim 51 corresponds to each of the species listed above.
The following claim(s) are generic: 48, 50-75, and 87-89.

The inventions listed as Groups I-IX do not relate to a single general inventive concept under PCT Rule 12.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Pursuant to 37 C.F.R. 1.475 (B-D), the ISA/US considers that where multiple products and processes are claimed, the main invention shall consist of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto.

Accordingly, the main invention (Group I) comprises the first method, a method for treating diabetes, and the first product using that method, a composition comprising a gastrin/CCK receptor ligand and a FACGINNT.

Group II does not share the same or corresponding technical feature because Group II is drawn to a different method that comprises different *ex vivo* method steps which are not coextensive and which do not share the same technical feature.

Group III does not share the same or corresponding technical feature because Group IV is drawn to a method for expanding and differentiating stem cells into insulin secreting cells in a diabetic recipient of implanted cell, which is a different method with steps and goals that are not coextensive and do not share the same technical feature.

Group IV does not share the same or corresponding technical feature because Group V is drawn to a method for reducing an amount of stem cells needed for transplant, which is a different method with steps and goals that are not coextensive and do not share the same technical feature.

Groups V and VI do not share the same or corresponding technical feature because each Group is drawn to a product which is a different combination of compounds than those of Group I and do not share the same technical feature. Each combination includes compounds which are not found in the other groups, and are structurally and functionally different chemical compounds. Each combination of compounds can be made and used without the other combinations, and thus do not relate to a single general invention concept within the meaning of PCT Rule 13.1.
Additionally, the composition of Group VI is formulated from unspecified components, and therefore encompasses combinations that comprise compounds that are structurally and functionally different chemicals from the compounds in the other combinations. Each combination of compounds can be made and used without the other combinations, and thus do not relate to a single general invention concept within the meaning of PCT Rule 13.1.

Group VII does not share the same or corresponding technical feature because Group VII is drawn to a method of reducing frequency of treating a diabetic subject by preparing a device for administering an I.N.T. composition, which is a different method with goals and method steps that do not share the same technical feature. Group VII requires a device for delivering a composition. The composition of Group VII is formulated from unspecified components, and therefore encompasses combinations that comprise compounds that are structurally and functionally different chemicals from the compounds in the other combinations. The device for delivering a composition of compounds can be made and used without the other combinations of the other groups, and thus does not relate to a single general invention concept within the meaning of PCT Rule 13.1.

Group VIII does not share the same or corresponding technical feature because it is drawn to a method with a goal similar to that of Group I but which includes a combination of compounds that are not coextensive with the combination of compounds of Group I and do not share the same technical feature.

Group IX does not share the same or corresponding technical feature because it is drawn to a different method with steps that are not coextensive and do not share the same technical feature.

The Authority therefore considers that the seven inventions do not share a special technical feature within the meaning of PCT Rule 13.2 and thus do not relate to a single general inventive concept within the meaning of PCT Rule 13.1

The species of gastrin/CCK receptor ligands, the species of FACGINTs, the species of agents for suppressing immune response, the species of implanted cells, and the species of EGF receptor ligands listed above do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each species is drawn to a compound or a cell which is a structurally and functionally different chemical compound or cell from the other species in the respective genus, each of which can be made, or isolated, and used without the other compounds or cells, and thus do not relate to a single general invention concept within the meaning of PCT Rule 13.1.

The species of measuring parameters listed above do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: each species is drawn to a variation in a method step, and each variation requires use of different compounds and different techniques which are not co-extensive, and thus do not relate to a single general invention concept within the meaning of PCT Rule 13.1.